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ORIGINAL REPORT

Risk of New Cancers After Radiotherapy in Long-Term Survivors of Retinoblastoma: An Extended Follow-Up

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ABSTRACT

Purpose
Many children diagnosed with retinoblastoma (Rb) survive into adulthood and are prone to subsequent cancers, particularly hereditary patients, who have germline *Rb-1* mutations. We have extended the follow-up of a large cohort of Rb patients for 7 more years to provide new information on the risk of additional cancers after radiotherapy in long-term survivors.

Patients and Methods
We analyzed the risk of new cancers through 2000 in 1,601 Rb survivors, diagnosed from 1914 to 1984, at two US medical centers. The standardized incidence ratio (SIR) was calculated as the ratio of the observed number of cancers after hereditary and nonhereditary Rb to the expected number from the Connecticut Tumor Registry. The cumulative incidence of a new cancer after hereditary and nonhereditary Rb and radiotherapy was calculated with adjustment for competing risk of death.

Results
Subsequent cancer risk in 963 hereditary patients (SIR, 19; 95% CI, 16 to 21) exceeded the risk in 638 nonhereditary Rb patients (SIR, 1.2; 95% CI, 0.7 to 2.0). Radiation further increased the risk of another cancer in hereditary patients by 3.1-fold (95% CI, 2.0 to 5.3). Hereditary patients continued to be at significantly increased risk for sarcomas, melanoma, and cancers of the brain and nasal cavities. The cumulative incidence for developing a new cancer at 50 years after diagnosis of Rb was 36% (95% CI, 31% to 41%) for hereditary and 5.7% (95% CI, 2.4% to 11%) for nonhereditary patients.

Conclusion
Hereditary Rb predisposes to a variety of new cancers over time, with radiotherapy further enhancing the risk of tumors arising in the radiation field.

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INTRODUCTION

Survivors of hereditary retinoblastoma (Rb), a rare childhood cancer of the eye caused by germline mutations of the *Rb-1* tumor suppressor gene, have an elevated risk of developing sarcomas, brain cancer, or melanoma, whereas survivors with nonhereditary Rb do not seem prone to secondary cancer.[1-8] Past studies of cancer incidence and mortality in our large cohort of 1-year survivors of Rb have revealed increased risks for these cancers in hereditary patients, especially after radiotherapy,[2,4] in addition to an increase in lipomas, a benign tumor of adipose tissue.[9] Recently, we reported an excess mortality of lung cancer in hereditary patients in our cohort, which suggested that carriers of the *Rb-1* mutation may be highly susceptible to smoking-induced lung cancer.[10] Because it is likely that the subsequent risk of cancer in hereditary Rb is sustained through adult life, we have continued to monitor this large cohort of Rb patients,[2,4] and in this report we provide new information on their cancer risk after 7 additional years of follow-up.

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PATIENTS AND METHODS

We had identified a total of 1,729 Rb patients diagnosed from 1914 to 1984 at two medical centers in New York and Boston. We excluded 114 patients (6.4%) who died within 12 months of diagnosis of Rb, 11 patients (0.6%) who died outside of the United States, two patients (0.1%) with an unknown birth year, and one patient (0.1%) who was determined not to have Rb, which left 1,601 (92.7%) 1-year survivors of Rb eligible for study. Data on medical history, family history of Rb, treatment for Rb, reports of additional cancers, and causes of death were collected from medical records, radiotherapy records, and three subsequent telephone interviews in 1987, 1993, and 2000.

We classified 963 (60%) patients with both eyes affected or only one eye affected and Rb in a family member as hereditary, and 638 (40%) patients with one eye affected and no known family member with Rb as nonhereditary. The larger proportion of hereditary to nonhereditary patients in this cohort is not typical of the pattern in the general population, in which 10% of hereditary patients inherit a germline mutation from an affected parent, 30% have a de novo germline mutation, and 60% have the nonhereditary form of Rb.[11] Among 10% to 15% of patients with one eye affected, a family history of Rb has been noted.[11] The difference in distribution in our cohort likely reflects differential referral of patients for treatment at well-known tertiary care centers.

Radiation Treatment for Rb

In our cohort, irradiated patients were treated with external-beam radiotherapy (90%), brachytherapy (1%), or a combination of both techniques (9%). The most common external-beam treatments in this cohort were a two-field technique with nasal and lateral fields, or a single-field technique, either lateral or anterior. Before 1960, external-beam energies were orthovoltage x-rays (35%). After 1960, energies were 22 to 23 MV betatron (34%), megavoltage photons (14%), and cobalt-60 (^{60}Co) gamma rays (8%). Tumor doses to the affected eye ranged from 15 to 115 Gy (average, 48 Gy), with the highest doses delivered from orthovoltage external-beam radiation machines. Brachytherapy before 1960 was delivered by plaques containing Rn-222 seeds (average, 200 mg hour radium [mgh Ra] equivalents; range, 160 to 400 mgh Ra equivalents), whereas in the later time period, ^{60}Co plaques were used (average, 400 mgh Ra equivalents; range, 150 to 800 mgh Ra equivalents).

Dosimetry data allowed us to place patients in three categories according to whether the second tumor site was heavily, moderated, or lightly irradiated. The dosimetry data were based on out-of-beam measurements in a water phantom combined with a three-dimensional mathematical anthropomorphic phantom.[12,13] Table 1 lists the distribution of scatter radiation doses from orthovoltage and betatron external beam for a typical Rb treatment for a 1-year-old patient.

About one third of patients were treated with chemotherapy either alone (3.5%) or in combination with radiotherapy (26.8%). However, data on type of chemotherapy used in this cohort are incomplete.

Follow-Up Procedures

We used various tracing sources (post office address correction updates, credit bureau searches, and social security administration mortality data; individual tracing; National Death Index) to update the vital status of the cohort before the most recent telephone survey in 2000. The Institutional Review Board of the National Institutes of Health approved this study, in which we surveyed patients or their families (for patients younger than 18 years) by telephone to update medical history, ascertain diagnoses of new cancers, and collect basic cancer risk factor information. Invasive cancers were confirmed by pathology reports (60.7%), hospital records or physician's records (20.6%), death certificates (15.5%), or autopsy reports (3.2%). Only confirmed invasive cancers, excluding nonmelanoma skin cancers, were included in the analysis. A trained nosologist coded all confirmed cancers according to the International Classification of Diseases for Oncology.[14]

Table 1. Radiation Scatter Doses After a Typical Treatment* for Retinoblastoma for a 1-Year-Old Patient

Organ Site†	Type of External-Beam Treatment	
	Orthovoltage‡ Dose (Gy)	Betatron§ Dose (Gy)
Brain (average)	3.60	1.60
Pineal gland	4.00	1.40
Eye plus orbit		
Untreated side	18.2	34.5
Treated side	60.0	45.0
Nasal region	34.0	3.20
Head and neck (soft tissue)		
Untreated side	9.00	5.50
Treated side	22.0	11.0
Facial bones	27.5	8.00
Salivary glands¶	4.25	1.60
Thyroid (average left and right)	2.00	0.90
Breast (average left and right)	0.40	0.40
Upper trunk	0.60	0.45
Lung (average left and right)	0.45	0.40
Kidney (average left and right)	0.13	0.28
Stomach	0.18	0.36
Pancreas	0.16	0.33
Liver	0.16	0.24
Colon	0.10	0.25
Bladder	0.07	0.19
Uterus	0.08	0.20
Rectum	0.07	0.19
Total active bone marrow	1.20	1.00

*Dose administered 50 Gy each to lateral and nasal field (4 cm × 4 cm) for orthovoltage and 50 Gy to one lateral field for betatron.
†Organs listed in descending order of distance from the treated eye.
‡Half-value layer = 1.9 mm Cu.
§23 MV photons.
¶Includes partotid, submaxillary, submandibular, and sublingual glands.

Statistical Analysis

Accrual of person-years of follow-up began 1 year after diagnosis of Rb and ended at the date the patient was last known to be alive, date of death, or December 31, 2000, whichever occurred earlier. The expected number of subsequent cancers among Rb patients was estimated based on age-specific, sex-specific, and calendar-year–specific cancer incidence rates from the Connecticut Tumor Registry. The state of Connecticut has the oldest continuous cancer registry in the United States, with incidence rates reported since 1935. For rates before 1935, the rates for 1935 to 1939 were used to estimate expected rates. The standardized incidence ratio (SIR) was calculated as the ratio of observed (O) cancers to the expected (E) number of cancers, and exact 95% CIs

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were calculated based on the Poisson distribution.[15] The excess absolute risk was calculated as the observed number of cancers minus the expected number of cancers divided by person-years times 10,000. We also calculated the cumulative incidence of a second cancer by type of Rb and treatment, with adjustment for competing risks of death according to the method of Gooley et al.[16]

RESULTS

Descriptive characteristics of the Rb cohort are listed in Table 2. The median year of RB diagnosis was 1966 for all patients. At the end of follow-up in 2000, 622 (64.6%) hereditary patients and 541 (84.8%) nonhereditary Rb patients were alive, 28 (2.9%) hereditary and 25 (3.9%) nonhereditary patients were lost to follow-up, and 313 (32.5%) hereditary patients and 72 (11.3%) nonhereditary patients had died. Follow-up since Rb diagnosis averaged 25.2 years for hereditary and 29.5 years for nonhereditary patients. At the last follow-up, 35% of nonhereditary and 22% of hereditary patients were age $\geq$ 40 years. Hereditary patients were typically treated with radiation for Rb (88%), whereas only 18% of nonhereditary patients were treated with radiotherapy. Nonhereditary patients were more often treated with surgery. In addition, chemotherapy was used alone or in combination with radiation for 41% of the hereditary patients and 13% of the nonhereditary patients.

In the 7 years since the last follow-up in 1993,[2] we have identified 78 new cancers after Rb, of which one half were sarcomas. There was a significantly elevated risk for all subsequent cancers among hereditary patients (SIR, 19; O, 260) but not among nonhereditary patients (SIR, 1.2; O, 17; Table 3). Among hereditary Rb patients, the risks were highest (SIR $>$ 100) for cancers of the bone and connective and soft tissue, eye and orbit, and nasal cavities. Risks were substantially elevated (SIR $>$ 10) for pineoblastoma, melanoma, and cancers of the brain and CNS, buccal cavity, and corpus uteri. In addition, significantly elevated risks (SIR $<$ 10) were noted for cancers of the lung, female breast,

Table 2. Selected Characteristics of 1-Year Survivors of Rb

Characteristic	Hereditary		Nonhereditary		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total No. of patients	963	100	638	100	1,601	100
Laterality						
Unilateral	47	4.9	638	100	685	42.8
Bilateral	916	95.1	0	0.0	916	57.2
Sex						
Male	512	53.2	334	52.3	846	52.8
Female	451	46.8	304	47.7	755	47.2
Age at Rb diagnosis, years						
$<$ 1	545	56.6	140	21.9	685	42.7
1	267	27.7	197	30.9	464	29.0
2	110	11.4	159	24.9	269	16.8
3-7	41	4.3	142	22.3	183	11.5
Year of Rb diagnosis						
1914-1949	106	11.0	75	11.8	181	11.3
1950-1959	200	20.8	100	15.7	300	18.7
1960-1969	312	32.4	198	31.0	510	31.9
1970-1979	253	26.3	192	30.1	445	27.8
1980-1984	92	9.5	73	11.4	165	10.3
Family history of Rb						
Yes	283	29.3	0	0.0	283	17.6
No	497	51.6	499	78.1	996	62.2
Uncertain	183	19.1	139	21.9	322	20.2
Treatment						
Surgery	94	9.8	480	75.2	574	35.8
Chemotherapy	16	1.6	40	6.0	56	3.5
Radiation	466	48.4	67	10.5	533	33.3
Radiation and chemotherapy	383	39.8	47	7.4	430	26.9
Unknown	4	0.4	4	0.9	8	0.7
Any radiotherapy						
Yes	849	88.2	114	17.5	963	60.0
No	114	11.8	524	82.5	638	40.0

Abbreviation: Rb, retinoblastoma.

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Table 3. Risk of New Cancers in 1-Year Survivors of Retinoblastoma by Hereditary Status

Cancer Site (ICD-O classification)	Hereditary (n = 963; person-years at risk, 25,309)				Nonhereditary (n = 638; person-years at risk, 18,972)			
	O	E	SIR*	95% CI	O	E	SIR	95% CI
All sites†	260	13.9	19	16 to 21	17	13.9	1.2	0.7 to 2.0
Bone (170)	75	0.21	360	283 to 451	0	0.16	0.0	0.0 to 22.6
Connective and soft tissue (171, 192.4, 192.5)	34	0.28	122	84 to 170	0	0.22	0.0	0.0 to 16.8
Nasal cavities (160)	32	0.03	1,111	760 to 1,569	0	0.03	0.0	0.0 to 135
Cutaneous melanoma (173 and M872-878)	29	1.05	28	18 to 40	0	1.00	0.0	0.0 to 3.7
Eye and orbit (190)	17	0.06	266	155 to 426	0	0.05	0.0	0.0 to 81
Brain, CNS (191, 192.0-192.3, 192.9)	10	0.74	13.6	6.5 to 25	2	0.58	3.43	0.4 to 12
Female breast (174)	10	2.52	3.96	1.9 to 7.3	7	2.46	2.84	1.1 to 5.9
Corpus uteri (182)	7	0.35	20	8.0 to 41	0	0.35	0.0	0.0 to 10
Buccal cavity (140-149)‡	7	0.34	20	8.2 to 42	0	0.37	0.0	0.0 to 9.9
Lung (162)	5	0.84	5.94	1.9 to 14	0	1.11	0.0	0.0 to 3.3
Pineoblastoma (194.4)	5	0.06	90.8	29 to 212	0	0.04	0.0	0.0 to 93
Colon (153)	3	0.48	6.28	1.3 to 18	0	0.58	0.0	0.0 to 6.3
Hodgkin's lymphoma (M9650-67)	3	0.88	3.4	0.7 to 10	1	0.70	1.4	0.04 to 8.0
Bladder (188, 189.9)	2	0.32	6.15	0.7 to 22	0	0.41	0.0	0.0 to 8.8
Thyroid (193)	2	0.60	3.34	0.4 to 12	2	0.53	3.78	0.4 to 14
Leukemia (204-207)	2	0.89	2.25	0.3 to 8.1	1	0.66	1.47	0.04 to 8.2
Excess absolute risk per 10,000 person-years§			97.2				1.63	

Abbreviations: SIR, standardized incidence ratio; O, observed; E, expected; ICD-O, International Classification of Diseases for Oncology.

*SIR is the ratio of O No. of subsequent (ie, second and third) cancers to E No. of cancers. E cancers as derived from Connecticut Tumor Registry.

†Cancer sites not listed for hereditary patients include two each of kidney (ICD-O 189.0) and other lymphoid tissue (ICD-O 202.2, 202.8); one each of small intestine (ICD-O 152.0) retroperitoneal tissue (ICD-O 158.0), male breast cancer (ICD-O 175.9), and abdomen, ill-defined (ICD-O 195.0); and nine of cancer, not otherwise specified (ICD-O 199.1). Cancer sites not listed for nonhereditary patients include one each of rectum (ICD-O 154.0); prostate (ICD-O 185.0); and two of cancer, not otherwise specified (ICD-O 199.1).

‡Buccal cavity for hereditary patients includes two each of cancer of the tongue (ICD-O 141; SIR, 25; 95% CI, 2.8 to 91) nasopharynx (ICD-O 147); (SIR, 47; 95% CI, 5.3 to 170), and three cancers of the salivary glands (ICD-O 142); (SIR, 49; 95% CI, 9.9 to 144).

§Excess risk, O minus E/person-years × 10,000.

and colon. Among the nonhereditary patients, only breast cancer was significantly increased in females (SIR, 2.8; O, seven), especially in those who received radiotherapy (SIR, 10; O, three). The excess absolute risk for a subsequent cancer after hereditary Rb was 97.2 per 10,000 person-years compared with 1.63 per 10,000 person-years for the nonhereditary Rb patients.

Among the small group of unilateral hereditary Rb patients (n = 47), there were seven cancers (two melanomas and one each of lung, breast, corpus uteri, connective tissue, and Hodgkin's lymphoma) resulting in an SIR of 7.31 (95% CI, 2.9 to 15; data not shown).

Table 4 indicates that the risk of subsequent cancer was elevated almost seven-fold in nonirradiated hereditary Rb patients, whereas radiotherapy further increased this risk by 3.1-fold (95% CI, 2.0 to 5.3). Among the irradiated, hereditary patients, the SIR was 22 (95% CI, 19 to 24) for all cancer sites combined, and the highest SIRs were noted for cancer in organs near or in the treatment field that were heavily irradiated (≥ 1 Gy). Among the hereditary patients, radiation treatment conferred more than twice the absolute excess risk of cancer compared with no radiation.

The overall risk of cancer after radiation and chemotherapy for hereditary Rb was 25 (95% CI, 21 to 30) compared with radiation without chemotherapy (SIR, 19; 95% CI, 16 to 23; data not shown). Most of this difference was accounted for by the higher risk noted for osteosarcomas after both chemotherapy and radiotherapy compared with radiotherapy alone (SIR, 539; 95% CI, 384 to 733 *v* SIR, 302; 95% CI, 205 to 428, respectively). There were no subsequent cancers noted among the 16 hereditary patients treated with chemotherapy only.

Among the irradiated hereditary Rb patients, 76% of all cancers diagnosed at age younger than 25 years were sarcomas, compared with 48% of all cancers that developed at age older than 25. For the nonirradiated hereditary Rb patients, 33% of all cancers diagnosed at age younger than 25 years were sarcomas, whereas only 8% of all tumors diagnosed at older ages were sarcomas. The bone cancers were mainly osteosarcomas (75 cases) of the skull and face (61%), lower limbs (29%), trunk (7.6%), and unknown location (3.8%). The connective tissue cancers included a variety of soft tissue sarcomas (80 cases) distributed across the head and face (70%), trunk (20%), lower limbs (3.8%), and unknown location (2.5%).

Notably, five of the seven uterine cancers were leiomyosarcomas (O/E, 376; 95% CI, 121 to 878), which are rare smooth muscle tumors that usually occur when patients are older than 50 years. The five uterine leiomyosarcomas were diagnosed in adults, ranging from age 31 to 47 years.

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Table 4. Risk of New Cancers in 1-Year Survivors of Hereditary Rb by Radiation for Rb

Cancer Site (ICD-O classification)	Radiation (n = 849; person-years at risk, 21,706)*				No Radiation (n = 114; person-years at risk, 3,602)			
	O	E	SIR*	95% CI	O	E	SIR	95% CI
All sites†	241	11.2	22	19 to 24	19	2.77	6.9	4.1 to 11
Heavily irradiated sites (≥ 1 Gy)								
Bone (170)	73	0.18	406	318 to 511	2	0.03	69	8.4 to 250
Soft tissue (171, 192.4, 192.5)	33	0.23	140	96 to 196	1	0.04	23	0.6 to 131
Nasal cavities (160)	32	0.02	1,364	933 to 1925	0	0.01	0.0	0.0 to 688
Eye and orbit (190)	17	0.05	312	181 to 499	0	0.01	0.0	0.0 to 392
Brain, CNS (191, 192.0-192.3, 192.9)	10	0.62	16	7.7 to 29	0	0.11	0.0	0.0 to 33
Pineoblastoma (194.4)	5	0.05	104	34 to 244	0	0.01	0.0	0.0 to 509
Buccal cavity (140-149)‡	7	0.27	26	10 to 53	0	0.07	0.0	0.0 to 54
Thyroid (193)	2	0.50	4.0	0.5 to 15	0	0.11	0.0	0.0 to 35
Moderately irradiated sites (0.4-1.0 Gy)								
Female breast (174)	8	1.91	4.2	1.8 to 8.2	2	0.61	3.3	0.4 to 12
Cutaneous melanoma (173 and M872-878)	26	0.85	30	20 to 45	3	0.20	15	3.1 to 44
Lung (162)	2	0.63	3.2	0.4 to 11	3	0.21	14	3.0 to 42
Leukemia (204-207)	1	0.76	1.3	0.03 to 7.3	1	0.13	7.8	0.2 to 43
Hodgkin's lymphoma (M9650-67)	1	0.75	1.3	0.03 to 7.4	2	0.13	16	1.9 to 56
Lightly irradiated sites (< 0.4 Gy)								
Corpus uteri (182)	5	0.25	20	6.4 to 46	2	0.10	20	2.5 to 74
Colon (153)	3	0.37	8.1	1.7 to 24	0	0.11	0.0	0.0 to 34
Bladder (188, 189.9)	2	0.25	7.9	0.9 to 28	0	0.07	0.0	0.0 to 52
Excess absolute risk per 10,000 person-years			105.9				45.1	

Abbreviations: Rb, retinoblastoma; SIR, standardized incidence ratio; O, observed; E, expected; ICD-O, International Classification of Diseases for Oncology.
*SIR is the ratio of O No. of subsequent (ie, second and third) cancers to E No. of cancers. Expected cancers derived from Connecticut Tumor Registry.
†Cancer sites not listed for irradiated patients include one each of other lymphoid tissue (ICD-O 202.2), retroperitoneal tissue (ICD-O 158.0), male breast cancer (ICD-O 175.9), and abdomen, ill-defined (ICD-O 195.0); two of kidney (ICD-O 189.0); and eight of cancer, not otherwise specified (ICD-O 199.1). Cancer sites not listed for nonirradiated patients include one each of small intestine (ICD-O 152.0) other lymphoma (ICD-O 202.8), and cancer not otherwise specified (ICD-O 99.1).
‡Buccal cavity for radiation patients includes two each of cancer of the tongue (ICD-O 141; SIR, 32; 95% CI, 3.5 to 114) and nasopharynx (ICD-O 147; SIR, 57; 95% CI, 6.3 to 204), and three cancers of the salivary glands (ICD-O 142; SIR, 60; 95% CI, 12 to 174).
§Excess risk, O minus E/person-years × 10,000.

The cumulative incidence of a second cancer at 50 years after diagnosis of Rb, adjusting for competing risk of death, was 36% (95% CI, 30.9% to 41.1%) for hereditary Rb compared with 5.69% (95% CI, 2.4% to 11%) for nonhereditary Rb (Fig 1). Among the hereditary patients, radiotherapy increased the cumulative probability of developing a second cancer to 38.2% (95% CI, 32.6% to 43.8%) at 50 years, whereas the cumulative probability was 21.0% (95% CI, 9.42 to 35.6%) for nonirradiated patients (Fig 2). After orthovoltage radiation, which was predominantly used before 1960, the cumulative incidence at 40 years for hereditary Rb patients was 32.9% (95% CI, 27% to 38.9%) compared with 26.3% (95% CI, 21.1% to 31.7%) for hereditary patients who were treated after 1960 with other types of external-beam radiation with less scatter radiation (Fig 3).

DISCUSSION

Consistent with earlier findings in this cohort,[2,4,10] hereditary Rb patients continued to have large excess risks of sarcomas and melanomas, as well as cancers of the nasal cavities, eye and orbit, brain, and lung. A radiation dose-response for sarcomas after hereditary Rb has been demonstrated previously in this and other cohorts.[2,17,18] The proportion of sarcomas diagnosed after Rb differed by age as well as by radiotherapy in this recent follow-up. About half of the tumors diagnosed when patients were older than 25 years were sarcomas among irradiated Rb patients, compared with 8% of tumors at this age among nonirradiated patients. A recent British study also reported a small proportion (14%) of sarcomas among all cancers in older, nonirradiated hereditary Rb patients.[19]

We detected an enhanced effect for the risk of osteosarcomas after radiation with chemotherapy compared to radiation alone, which is consistent with the previous findings of Tucker et al.[17]

Radiotherapy likely contributed to the significantly increased risks that we observed for cancers of the brain, nasal cavities, and eye and orbit. All of the brain and the majority of the eye cancers were diagnosed in patients older than 5 years, whereas four of five pineoblastomas were diagnosed in patients younger than 5 years. No additional

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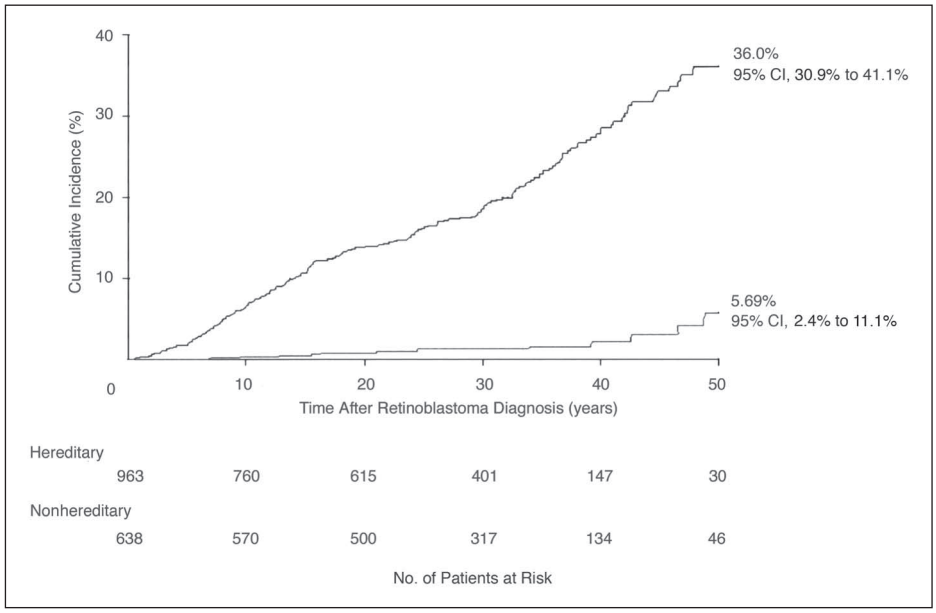

Fig 1. Cumulative incidence and 95% CIs of new cancers by time since diagnosis of retinoblastoma by hereditary status.

pineoblastomas, or trilateral retinoblastomas as they are often classified, have been diagnosed since the last follow-up of this cohort. This was not unexpected because these tumors are typically diagnosed at very young ages after Rb and the most recent year of Rb diagnosis in this cohort was 1984. In addition, it has been suggested that the declining incidence of pineoblastomas in another series of Rb patients may be due to the declining use of external-beam radiation therapy,[20] which supports the notion that high-dose radiotherapy is probably related to the earlier excess that we observed. Alternatively, it has been hypothesized that chemoreduction with a three-drug protocol, which has been used since 1995, might explain the more recent decrease in pineoblastoma incidence after Rb at another institution.[21]

The increased risk for melanoma, which was noted in our previous studies,[2,4] continued, probably due to genetic factors independent of radiation, because risks were elevated in both irradiated and nonirradiated patients.

Our report of an increased lung cancer risk in hereditary Rb patients[10] was confirmed recently by a cohort of nonirradiated Rb patients in the United Kingdom.[19] Somatic mutations in the *Rb-1* gene are known to contribute to

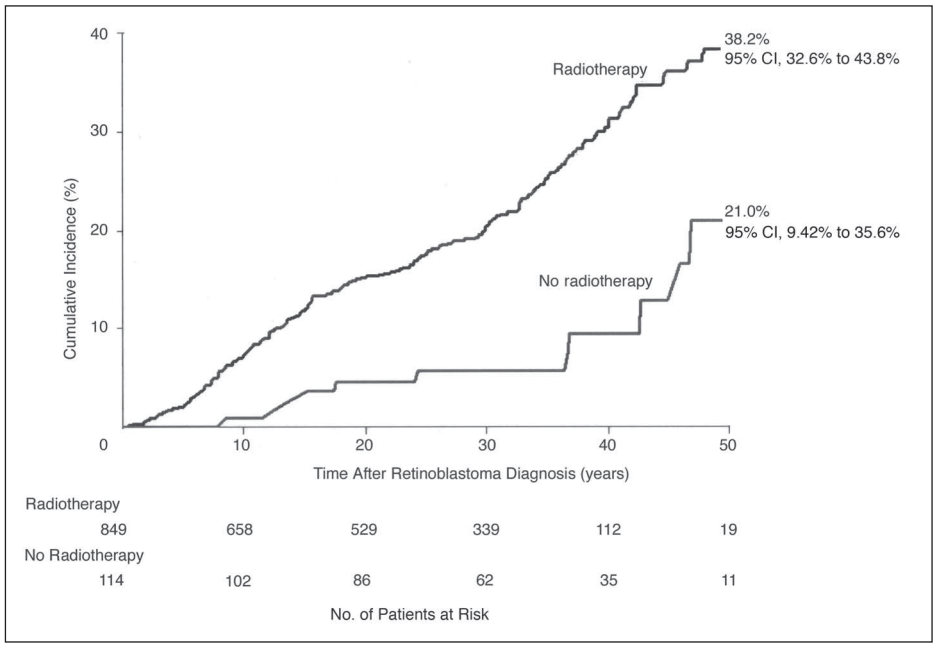

Fig 2. Cumulative incidence and 95% CIs of new cancers by time since diagnosis of hereditary retinoblastoma by radiotherapy.

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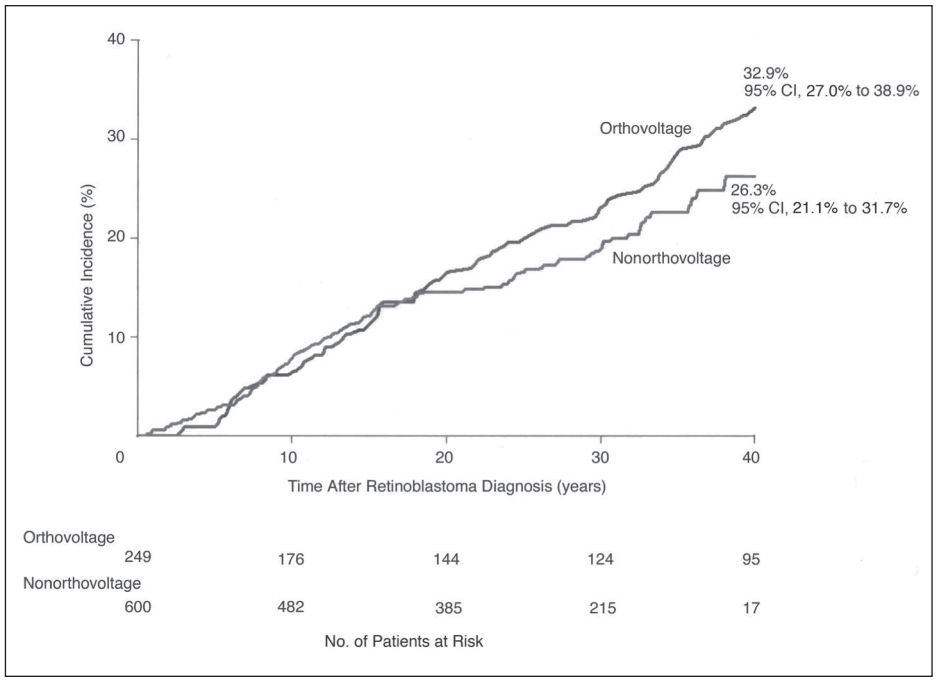

Fig 3. Cumulative incidence and 95% CIs of new cancers by time since diagnosis of hereditary retinoblastoma by orthovoltage radiotherapy.

the development of lung cancer,[22] and smoking information in our cohort suggested that Rb patients may have an increased susceptibility to the carcinogenic effects of tobacco smoke.[10]

At the time of last follow-up, the excess risk of breast cancer seemed limited to nonhereditary Rb.[2] With additional follow-up, risks were similarly increased for irradiated patients with hereditary and nonhereditary Rb. Breast dose from scatter radiation after treatment for Rb was approximately 0.4 Gy. The risk of radiation-related breast cancer is known to be heightened when the exposure occurs at very young ages, as observed after irradiation for enlarged thymus glands (mean dose, 0.7 Gy) or hemangioma (mean dose, 0.5 Gy), and exposure to the atomic blasts in Japan (mean dose, 0.3 Gy).[23] It is interesting that an epithelioid leiomyosarcoma of the breast was noted after radiotherapy for hereditary Rb in a 33-year-old male in our series.

In our updated follow-up of hereditary Rb patients, new excess risks emerged for cancers of the salivary gland, tongue, and nasopharynx after radiotherapy, based on small numbers. Cancer of the salivary gland has been linked previously to radiotherapy during childhood for tinea capitis (mean dose, 0.4 Gy) and enlarged tonsils (mean dose, 4.6 Gy),[24] which is consistent with dose received by Rb patients (1.6 to 4.2 Gy). Salivary gland cancer has been noted after radiation (10 to 13 Gy) associated with bone marrow transplantation in children, but the role of radiation is unclear in the increased risk of tongue cancer after bone marrow transplantation.[25] Cancer of the tongue was diagnosed at age 10 in a hereditary Rb patient, who was treated with brachytherapy.[26] In our cohort, cancer of the tongue was diagnosed at ages 19 and 42 years. Cigarette smoking has been associated with cancer of the tongue,[27] however, neither of the two patients in our cohort smoked. Doses to the nasal region were high (3.2 to 34 Gy) in our series, and the two nasopharyngeal cancers included an osteosarcoma of the hard palate and carcinoma of the nasopharynx, not otherwise specified.

Also noted for the first time were excess risks of cancers of the colon and corpus uteri among the hereditary patients. Five of the seven uterine cancers and two of the three colon cancers were leiomyosarcomas. Risks were similarly increased in patients with and without prior radiotherapy for RB, which is consistent with genetic susceptibility to a variety of sarcomas in Rb patients.[28,29]

In another series of long-term hereditary Rb survivors not treated with radiation,[19] bladder cancer was significantly elevated and presumably attributed to tobacco smoking, although smoking data were not available. The risk of this tumor was markedly but not significantly increased in Rb patients in our study. One of the two bladder cancer patients was a nonsmoker, and the smoking status of the second patient is unknown.

In our extended follow-up, the cumulative incidence for developing a new cancer at 50 years after hereditary Rb, adjusting for competing risk of death, was 36%. As the Rb patients have aged, the competing risk of death has increased to 33% at 50 years for hereditary Rb and 11% for nonhereditary Rb. We had previously reported the Kaplan-Meier probability of developing a new malignancy of 51% at 50 years after hereditary Rb in this cohort, whereas both the cumulative incidence as well as the Kaplan-Meier

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probability was 5.7% for nonhereditary Rb.[2] The lack of adjustment for competing risks with the Kaplan-Meier statistic may explain some of the differences in these risk estimates between 1993 and 2000. The lower cumulative risk of a new cancer through 2000 for hereditary Rb patients compared with the earlier follow-up in 1993 with Kaplan-Meier probabilities is encouraging because it probably reflects in part the lower doses of scatter radiation received by patients after 1960. This is supported by the somewhat lower cumulative incidence of new cancers among patients treated with non–orthovoltage radiation compared with those patients treated with orthovoltage radiation. However, the persistently elevated cancer risk in hereditary but not nonhereditary Rb points to the role of germline *Rb-1* mutations in a variety of secondary tumors, and emphasizes the need for life-long surveillance for subsequent cancers in hereditary Rb patients, especially those treated with radiation.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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